

# **EFFECTS OF RADIATION AND DIETARY IRON ON EXPRESSION OF GENES AND PROTEINS INVOLVED IN DRUG METABOLISM**

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## **INTRODUCTION**

Liver function, especially the rate of metabolic enzyme activities, determines the concentration of circulating drugs and the duration of their efficacy. Most pharmaceuticals are metabolized by the liver, and clinically-used medication doses are given with normal liver function in mind. A drug overdose can result in the case of a liver that is damaged and removing pharmaceuticals from the circulation at a rate slower than normal. Alternatively, if liver function is elevated and removing drugs from the system more quickly than usual, it would be as if too little drug had been given for effective treatment. Because of the importance of the liver in drug metabolism, we want to understand any effects of spaceflight on the enzymes of the liver.

Dietary factors and exposure to radiation are aspects of spaceflight that are potential oxidative stressors and both can be modeled in ground experiments. In this experiment, we examined the effects of high dietary iron and low dose gamma radiation (individually and combined) on the gene expression of enzymes involved in drug metabolism, redox homeostasis, and DNA repair.

## **METHODS**

All procedures were approved by the JSC Animal Care and Use Committee. Male Sprague-Dawley rats were divided into 4 groups (n=8); control, high Fe diet (650 mg iron/kg), radiation (fractionated 3 Gy exposure from a Cs-137 source) and combined high Fe diet + radiation exposure. Animals were euthanized 24h after the last treatment of radiation; livers were removed immediately and flash-frozen in liquid nitrogen. Expression of genes thought to be involved in redox homeostasis, drug metabolism and DNA damage repair was measured by RT-qPCR. Where possible, protein expression of the same genes was measured by western blotting. All data are expressed as % change in expression normalized to reference gene expression; comparisons were then made of each treatment group to the sham exposed/ normal diet control group. Data was considered significant at  $p < 0.5$ .

## **RESULTS**

Among the redox homeostasis genes examined, metallothionein showed a significant down regulation in the radiation treated group (-3.85 fold) and a trend toward down regulation in the high Fe + rad group. Metallothionein is involved in the regulation of physiological metals and also has antioxidant activities.

Among the drug metabolism genes examined, ATP binding cassette subfamily B (Abcb1b) gene expression increased more than 10-fold in both groups that received radiation treatments. This increased expression was also seen at the protein level. This ABC transporter carries many different compounds across cell membranes, including administered medications. The cytochrome P450 2E1 enzyme, a mixed-function oxidase that deactivates some medications and activates others, showed about a 2-fold increase in gene expression in both radiation-treated groups, with a trend toward increased expression at the protein level. Expression of epoxide hydrolase, which detoxifies polycyclic aromatic hydrocarbons, showed similar 2-fold increases.

Among the DNA repair genes examined, expression of RAD51 was significantly down regulated (1.5 fold) in the radiation treated group. RAD51 is involved in repair of double-stranded DNA breaks.

## **CONCLUSION**

This experiment used 2 different sources of physiological oxidative stress, administered separately and together, and examined their impacts on liver gene and protein expression. It is clear that significant changes occurred in expression of several genes and proteins in the radiation-treated animals. If the results from this ground analog of portions of the spaceflight environment hold true for the spaceflight environment itself, the physiological roles of the affected enzymes (drug transport and metabolism, redox homeostasis) could mean consequences in redox homeostasis or the pharmacokinetics of administered medications.